

**REMARKS**

Claims 2-4 and 6-15 are pending in this application. Non-elected claims 11-15 have been withdrawn from consideration by the Examiner. By this Amendment, claims 2, 4, and 6 are amended and claims 1 and 5 are canceled. Support for the amendments to the claims may be found, for example, in the specification at page 5, lines 18-21, page 4, lines 23-33, and page 11, line 22 to page 12, line 39. No new matter is added.

**I. Personal and Telephone Interviews**

The courtesies extended to Applicants' representative by Examiner Kolker at the personal interview held March 5, 2009 and during the telephone interview held March 6, 2009, are appreciated. The reasons presented at the interviews as warranting favorable action are incorporated into the remarks below, which constitute Applicants' record of the interviews.

**II. Information Disclosure Statement**

The Office Action notes that the listing of references in the specification is not a proper Information Disclosure Statement. Applicants note that in the September 1, 2006 Information Disclosure Statement, the references listed in the specification on page 57 were properly submitted. These references were in turn acknowledged with the September 11, 2008 Office Action.

**III. Allowable Subject Matter**

The Office Action, on page 7, indicates that claims 8 and 9 recite allowable subject matter. Specifically, these claims are indicated as allowable if rewritten in independent form to include all of the features of the base claim and any intervening claims. Applicants appreciate this indication of allowability, but respectfully submit that at least claim 2, from which these claims depend, and the other claims depending from claim 2 are also allowable for at least the reasons indicated below.

**IV. 35 U.S.C. §102 Rejection**

The Office Action rejects claims 2-3 and 10 under 35 U.S.C. §102(b) as allegedly being anticipated by WO 01/05422 to Roecklin as evidenced by U.S. Patent No. 7,081,345 ("Roecklin"). Applicants respectfully traverse the rejection.

**A. Claim 2**

Without conceding the propriety of the rejection, claim 2 is amended to recite:

2. A method specifically for detecting and/or quantifying a cytotoxic factor having a gliotoxic activity, associated with multiple sclerosis, in a biological sample, comprising isolating a heterocomplex chosen from the heterocomplex GM2AP/GM2/MRP14 and mutated GM2AP/GM2/MRP14, in which mutated GM2AP corresponds to the sequence SEQ ID No. 2, from said biological sample.

It is well settled that a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.

See MPEP §2131. Roecklin does not teach each and every element of claim 2.

The Office Action asserts that the starting materials and procedures detailed in Roecklin are the same as those that appear in Example 2 of the present specification. However, as discussed during the telephone interview, Example 2 of the present specification does not, nor is it asserted to, provide a suitable method to isolate the cytotoxic heterocomplex from urine. Example 2 discloses a process for purifying and isolating proteins, not protein-lipid heterocomplexes. Specifically, it involves the following steps: 1) providing urine samples from MS patients and from normal donors; 2) protein-enrichment of the samples by precipitation with ammonium sulfate; 3) ion-exchange chromatography of the protein enriched samples and selecting the fractions positive to the MTT assay; 4) purification; and 5) separating and staining the protein bands and then subjecting the protein bands to proteolysis in a trypsin solution. In Example 3 of the present specification, the samples obtained in Example 2 are analyzed. See Table 1, specification at pages 23-24.

The steps outlined in Examples 2 and 3 of the present specification result in the isolation of the proteins GM2AP and MRP14. These procedures are designed to eliminate lipids and to purify proteins and, therefore, these steps could not result in the isolation of the heterocomplex of claim 2, as specifically stated in the specification at page 38, line 35 to page 39, line 2.

As discussed during the personal interview, the teachings of Roecklin, specifically Examples 1-8, correspond at least in part to Examples 2 and 3 of the present specification. However, as discussed above, Examples 2 and 3 of the present specification do not disclose the isolation of the heterocomplex of claim 2. Rather, the isolation and detection of the heterocomplex is described in the procedures and protocols outlined in Examples 8-11. Roecklin does not teach or suggest a method of isolating a protein-lipid heterocomplex and, thus, fails to teach each and every element of claim 2.

**B. Claim 3**

The Office Action asserts that Roecklin anticipates claim 3 because it asserts that Roecklin teaches the detection of GM2AP, and that because GM2AP is a component of the cytotoxic factor, the cytotoxic factor may thus be detected with anti-GM2AP antibody. *See* Roecklin, Example 14, columns 54-55. Applicants respectfully disagree.

The heterocomplex of claim 2 cannot be specifically detected by using anti-GM2AP antibody. As shown in Example 8 of the present specification, this specific detection can be carried out by the combined use of at least both anti-GM2AP antibody and anti-MRP14 antibody or by one antibody specific to the heterocomplex. When only one antibody is used, it is specific to the heterocomplex, and recognizes neither GM2AP, nor mutated GM2AP, nor MRP14, as shown in the last part of Example 9 of the present specification. Thus, Roecklin does not teach each and every element of claim 3.

**C. Conclusion**

Roecklin does not anticipate claim 2 or claim 3. Claim 10 depends from claim 2 and, thus, also is not anticipated by Roecklin. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

**V. 35 U.S.C. §103 Rejection**

**A. Roecklin and Hornbeck**

The Office Action rejects claims 2-5 and 10 under 35 U.S.C. §103(a) over Roecklin in view of Hornbeck et al., *Enzyme-Linked Immunosorbent Assays*, Current Protocols in Molecular Biology, 11.2.1 - 11.2.22 (2000) ("Hornbeck"). By this Amendment, claim 5 is canceled, rendering its rejection moot. As to the remaining claims, Applicants respectfully traverse the rejection.

The deficiencies of Roecklin with respect to claim 2 have been discussed above. Hornbeck does not, nor is it asserted to, cure all the deficiencies of Roecklin. Claim 2 would not have been rendered obvious by the combination of Roecklin and Hornbeck. Claims 3, 4 and 10 depend from claim 2 and, thus, also would not have been rendered obvious by the combination of applied references. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

**B. Roecklin, Hornbeck, and Perron**

The Office Action rejects claims 2-7 and 10 under 35 U.S.C. §103(a) over Roecklin in view of Hornbeck and further in view of Perron et al., *Glial cytotoxicity evidenced in multiple sclerosis patients is caused by a proteolipidic complex made of S100 calcium binding protein MRP-14, GM2 activator protein and GM2 ganglioside*, 10 Journal of Neurovirology (Suppl. 3) 124 (2004) ("Perron"). By this Amendment, claim 5 is canceled rendering its rejection moot. As to the remaining claims, Applicants respectfully traverse the rejection.

The deficiencies of Roecklin and/or Hornbeck with respect to claim 2 have been previously discussed. Perron does not, nor is it asserted to, cure all of the above-described deficiencies of Roecklin and Hornbeck. Claim 2 would not have been rendered obvious by Roecklin, Hornbeck, and Perron. Claims 3, 4, 6, 7 and 10 variously depend from claim 2 and, thus, also would not have been rendered obvious by the combination of applied references. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

**VI. Double Patenting**

**A. Copending Application No. 11/450,360**

The Office Action provisionally rejects claims 2-5 and 10 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 76 and 77 of copending Application No. 11/450,360. Because the cited copending application has not issued, filing a Terminal Disclaimer to obviate a provisional double-patenting rejection is premature. See MPEP §706.02(k). Applicants respectfully request abeyance of the double patenting rejection.

**B. Roecklin**

The Office Action rejects claims 2-5 and 10 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 8 and 9 of U.S. Patent No. 7,081,345 ("Roecklin"). By this Amendment, claim 5 is canceled, rendering its rejection moot. As to the remaining claims, Applicants respectfully traverse the rejection.

The deficiencies of Roecklin with respect to the present claims is discussed above. Roecklin does not teach or suggest and would not have rendered obvious the present claims. Therefore, claims 2-4 and 10 are patentably distinct from claims 8 and 9 of Roecklin. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

**VII. Rejoinder**

Applicants also respectfully request rejoinder of non-elected method claims 11–15. National stage applications filed under 35 U.S.C. §371 are subject to unity of invention practice as set forth in PCT Rule 13, and are not subject to U.S. restriction practice. *See* MPEP §1893.03(d). Because this application is a national stage, unity of invention practice applies. Claims 11-15 share at least the common special technical feature of the heterocomplex GM2AP/GM2/MRP14 and, thus, unity of invention exists. Because the method claims are believed to be allowable for at least the reasons presented above, and because all the pending claims share a common special technical feature, Applicants respectfully request withdrawal of the Restriction Requirement and rejoinder of claims 11–15.

**VIII. Conclusion**

In view of the foregoing, it is respectfully submitted that this application is in condition for allowance. Favorable reconsideration and prompt allowance of the application are earnestly solicited.

Should the Examiner believe that anything further would be desirable in order to place this application in even better condition for allowance, the Examiner is invited to contact the undersigned at the telephone number set forth below.

Respectfully submitted,



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